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Symptom Management and Supportive Care

Treatment of Dexamethasone-Induced Hiccup in Chemotherapy Patients by Methylprednisolone Rotation

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Dexamethasone • Hiccup • Methylprednisolone • Corticosteroids

Abstract

Background. Dexamethasone-induced hiccup (DIH) is an underrecognized symptom in patients with cancer, and little information is available about its treatment. The aims of this study were to investigate the feasibility of methylprednisolone rotation as treatment and to confirm the male predominance among those with cancer who experienced DIH during chemotherapy.

Methods. Persons with cancer who experienced hiccups during chemotherapy treatment and who were receiving treatment with dexamethasone were presumed to have DIH. The following algorithmic practice was implemented for antiemetic corticosteroid use: rotation from dexamethasone to methylprednisolone in the next cycle and dexamethasone re-administration in the second cycle of chemotherapy after recognition of hiccups to confirm DIH. All other antiemetics except corticosteroid remained unchanged. Patients ($n = 40$) were recruited from eight cancer centers in Korea from September 2012 to April 2013. Data were collected retrospectively.

Results. Hiccup intensity (numeric rating scale [NRS]: 5.38 vs. 0.53) and duration (68.44 minutes vs. 1.79 minutes) were significantly decreased after rotation to methylprednisolone, while intensity of emesis was not increased (NRS: 2.63 vs. 2.08). Median dose of dexamethasone and methylprednisolone were 10 mg and 50 mg, respectively. Thirty-four (85%) of 40 patients showed complete resolution of hiccups after methylprednisolone rotation in the next cycle. Of these 34 patients, 25 (73.5%) had recurrence of hiccups after dexamethasone re-administration. Compared with baseline values, hiccup intensity (NRS: 5.24 vs. 2.44) and duration (66.43 minutes vs. 22.00 minutes) were significantly attenuated after dexamethasone re-administration. Of the 40 eligible patients, 38 (95%) were male.

Conclusion. DIH during chemotherapy could be controlled without losing antiemetic potential by replacing dexamethasone with methylprednisolone. We also identified a male predominance of DIH. Further prospective studies are warranted.

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Implications for Practice: Dexamethasone, an essential antiemetic for chemotherapy, may cause hiccups, and dexamethasone-induced hiccup (DIH) happens frequently. Discontinuance of dexamethasone can relieve DIH; however, abrupt suspension of dexamethasone in patients on emetogenic chemotherapy increases the risk for emesis in return. In this study, we introduce a new treatment strategy, dexamethasone rotation into methylprednisolone, that may offer a solution to this dilemma. Our data show that a majority of patients experienced a reduction in hiccup without aggravating emesis by switching to methylprednisolone. This treatment strategy has not been previously reported except in a case series by our team. The treatment maneuver described in this study has the potential to improve quality of life in cancer patients undergoing chemotherapy.

Introduction

Dexamethasone is an essential agent for preventing chemotherapy-induced emesis. Various guidelines recommend dexamethasone as a prerequisite medication in almost all antiemetic regimens [1]. Dexamethasone may cause adverse events including fatigue, sleep disturbance, and hiccups. Of these adverse events, dexamethasone-induced hiccup (DIH)

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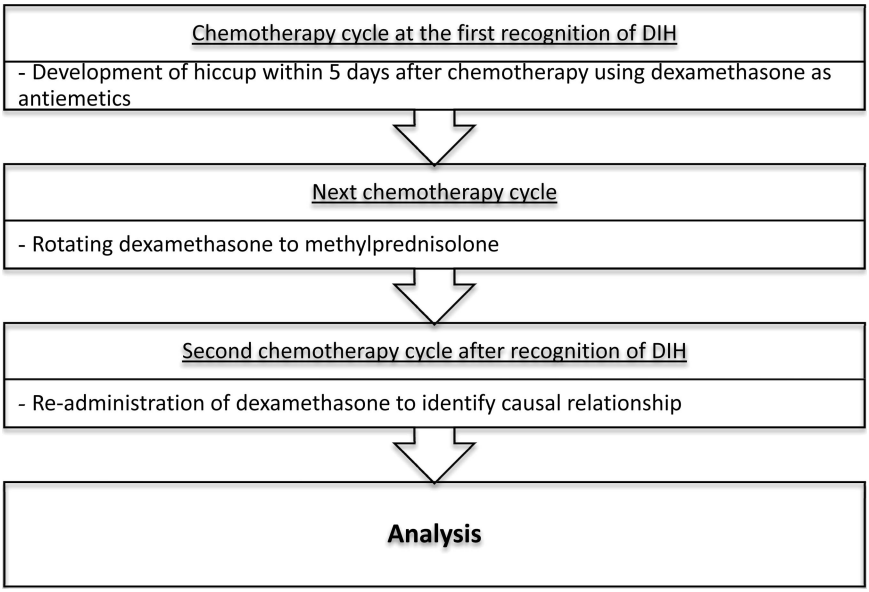

Figure 1. Diagram of the study concept.

is likely to be regarded as a minor, transient source of discomfort. However, persistent hiccups can lead to a number of distressful symptoms such as insomnia, depression, and dyspnea. Although the incidence of DIH is unclear, patients may have hiccups more often than clinicians assume because of underreporting and underrecognition of the problem [2].

The hiccup reflex arc is composed of afferent and efferent nerves and a central part. The afferent limb is composed of vagus nerves, phrenic nerves, and a sympathetic chain from T6 to T12. Numerous factors such as cancer invasion and chemicals that irritate nerves belonging to the afferent limb can provoke hiccups. The central limb is composed of nerves in the spinal cord (C3 to C5) that connect to the respiratory center, medullary reticular formation, phrenic nerve nuclei, and hypothalamus. Hiccups may also be caused by drugs or treatments that influence the hiccup center in this area. According to the proposed mechanism of DIH, dexamethasone lowers the threshold for synaptic transmission in the midbrain and ultimately induces hiccups [3].

Discontinuation of dexamethasone can be an alternative for relieving DIH. However, abrupt suspension of dexamethasone in patients on emetogenic chemotherapy elevates the risk for emesis [4]. Meanwhile, many studies have indicated that methylprednisolone is an effective antiemetic, either alone or in combination with serotonin antagonists [5–8]. We recently reported cases that suggest that rotating dexamethasone and methylprednisolone may be a solution to this perplexing issue [9]. Moreover, we observed an interesting male predominance among patients who experienced DIH in the study. Previous studies support our observation that DIH usually occurs in males [9–14]. However, the patient cohort was limited to a case series, and little information about objective assessments of intensity was available. The aim of this study was to investigate the efficacy of methylprednisolone rotation and to confirm male predominance among those receiving cancer chemotherapy who experienced DIH.

Methods

Patient Eligibility

We shared information with physicians in Korea who treat cancer that dexamethasone could cause hiccups, and we introduced the concept of sequential methylprednisolone and dexamethasone re-administration in patients with presumed DIH (Fig. 1) at medical conferences from June 2012 to August 2012. Re-administration of dexamethasone was needed to identify the causative agent for hiccups because numerous factors are associated with hiccup [15]. Physicians at eight cancer centers applied this algorithmic practice when hiccups developed during chemotherapy. Physicians gave patients a detailed explanation regarding dexamethasone as a possible cause of their hiccups and the necessity of administering dexamethasone.

A retrospective patient cohort was derived from all patients with solid cancers (age $>$18 years) on chemotherapy who received dexamethasone as an antiemetic from September 2012 to April 2013. Patient demographic data, including age, sex, intent of chemotherapy, chemotherapeutic regimen, and cancer diagnosis, were retrieved from each institution's electronic database. Data were collected from eight cancer centers in Korea. The following eligibility criteria were applied: hiccups developed within five days after starting chemotherapy; dexamethasone was replaced with methylprednisolone as an antiemetic in the next chemotherapy cycle; and dexamethasone was re-administered in the cycle after methylprednisolone administration to identify a causal relationship between hiccups and dexamethasone. All other antiemetics except corticosteroid were used following each institution's own protocol in every chemotherapeutic cycle and therefore remained unchanged over the study period.

Patients with brain metastases or hiccups before dexamethasone administration were excluded. Our analysis focused on determining whether methylprednisolone rotation

Table 1. Baseline characteristics of patients with DIH

Characteristic	Category	Number	Percent
Age	Median (range)	58 years (36–80 years)	
Gender	Male	38	95
	Female	2	5
Primary cancer site	Gastrointestinal	22	55
	Lung	6	15
	Hepatobiliary	4	10
	Genitourinary	1	3
	Other	7	17
Chemotherapy intent	Adjuvant	14	35
	Palliative	21	52
	Curative[a]	5	13
ECOG performance status	0	12	30
	1	25	63
	2	3	7
Chemotherapeutic regimen	Cisplatin-containing	26	65
	Irinotecan-containing	5	13
	Oxaliplatin-containing	7	18
	Other	2	4
Chemotherapy cycle in which hiccups developed	First	21	53
	Second	7	17
	Third	5	13
	Fourth	7	17
Dexamethasone (mg)	Median (range)	10 (4–20)	
Methylprednisolone (mg)	Median (range)	50 (20–100)	
Symptom intensity (NRS, median)	Hiccup (minimum-maximum)	5 (1–10)	65
	Duration/episode, minutes (range)	10 (1–720)	13
	Emesis (minimum-maximum)	2.5 (0–10)	18

[a]Radiation was delivered simultaneously.
Abbreviations: DIH, dexamethasone-induced hiccup; ECOG, Eastern Cooperative Oncology Group; NRS, numeric rating scale.

could resolve DIH and maintain antiemetic effectiveness in patients undergoing chemotherapy. The protocol was approved by our institutional review board.

Assessment

The Edmonton Symptom Assessment System includes pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, anorexia, well-being, and one patient-specific symptom [16]. The severity of each symptom at the time of assessment is rated from 0 to 10 on a numeric rating scale (NRS), with 0 indicating that the symptom is absent and 10 indicating the worst possible symptom severity. The intensities of hiccups and emesis were also assessed using an NRS. Patients were asked about their average scores for hiccups and emesis during the 24 hours prior to the time of evaluation.

Statistical Analysis

Descriptive statistics (means, medians, and percentages) were used to summarize the demographic characteristics of the patients. A paired *t* test was used to compare the intensities of hiccups and emesis between the dexamethasone and methylprednisolone cycles. The demographic and clinical characteristics of the patients according to median DIH intensity (NRS <5 vs. ≥ 5) were compared using a chi [2] test, Fisher exact test, or Mann-Whitney *U* test. Two-sided *p* values $<.05$ indicated significance. The Statistical Package for the Social Sciences (SPSS, version 18.0; SPSS software, IBM Corp., Armonk, NY, http://www-01.ibm.com/software/analytics/spss/) was used for the statistical analyses.

Results

Baseline Characteristics

Patient baseline demographic and clinical characteristics related to DIH are listed in Table 1. The 40 patients (38 men and 2 women) recruited from eight centers had a median age of 58 years (range, 36–80 years). Gastrointestinal cancer was the most common malignancy ($n = 22$, 55%) followed by lung cancer ($n = 6$, 15%). Almost all patients ($n = 39$, 97.5%) received the same chemotherapeutic agents during the study period. DIH usually occurred in an early cycle of chemotherapy (first cycle, $n = 21$, 53%; second cycle, $n = 7$, 17%). The median daily dose of dexamethasone and methylprednisolone was 10 mg and 50 mg, respectively. The patients were divided into two groups according to median hiccup intensity (NRS <5 vs. ≥ 5) and analyzed to iden-

Table 2. Baseline characteristics according to hiccup intensity

Characteristic	Category	NRS <5 ($n = 13$)	NRS ≥5 ($n = 27$)	p
Age (years)	Median (range)	60.00 (36–80)	58.00 (42–74)	.909
	<65	9 (22.5%)	21 (52.5%)	.700
	≥65	4 (10.0%)	6 (15.0%)	
Gender	Male	11 (27.5%)	27 (67.5%)	.100
	Female	2 (5.0%)	0 (0%)	
Primary cancer site	Gastrointestinal	7 (17.5%)	15 (37.5%)	1.000
	Nongastrointestinal	6 (15.0%)	12 (30.0%)	
Radiation exposure	Concurrent radiation	2 (5.0%)	3 (7.5%)	.985
	Chemotherapy alone	11 (27.5%)	24 (60.0%)	
ECOG performance status	0	2 (5.0%)	10 (25.0%)	.271
	1–2	11 (27.5%)	17 (42.5%)	
Chemotherapeutic regimen	Cisplatin-containing	7 (17.5%)	19 (47.5%)	.480
	Non-cisplatin-containing	6 (15.0%)	8 (20.0%)	
Chemotherapy cycle in which hiccup developed	First	7 (17.5%)	13 (32.5%)	1.000
	Second or more	6 (15.0%)	14 (35.0%)	
Dexamethasone (mg)	Median (range)	10 (8–20)	10 (4–20)	.376
	Emesis (minimum–maximum)	1.5 (0–6)	3 (0–10)	.345

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NRS, numeric rating scale.

Table 3. Hiccup and emesis changes depending on corticosteroids in patient cohort ($n = 40$)

	Baseline (dexamethasone)		Rotation (methylprednisolone)			Re-administration (dexamethasone)		
Variable	Mean (SD)	95% CI	Mean (SD)	95% CI	p (baseline vs. rotation)	Mean (SD)	95% CI	p (rotation vs. re-administration)
Hiccup intensity (NRS)	5.38 (2.37)	4.64–6.12	0.53 (1.36)	0.09–0.96	<.001	2.50 (2.61)	1.66–3.34	<.001
Hiccup duration (minutes)	68.44 (150.12)	14.31–122.56	1.79 (9.73)	−1.41–4.99	.017	21.50 (90.05)	−8.97–51.97	.165
Emesis intensity (NRS)	2.63 (2.31)	1.89–3.36	2.08 (2.18)	1.38–2.77	.104	2.05 (1.97)	1.42–2.68	.935

Abbreviations: CI, confidence interval; NRS, numeric rating scale; SD, standard deviation.

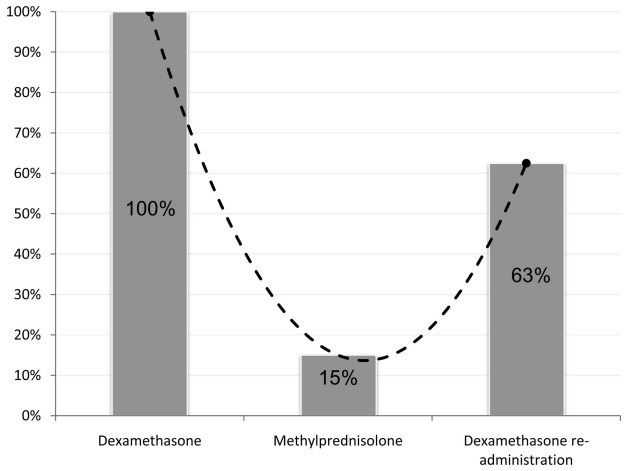

Figure 2. Change of hiccup incidence ($n = 40$).

tify factors affecting hiccup intensity (Table 2). No statistical differences were found between dose level of dexamethasone and hiccup intensity.

Hiccup and Emesis Changes

Hiccup intensity (NRS: 5.38 vs. 0.53, $p < .001$) and duration (68.44 minutes vs. 1.79 minutes, $p = .017$) were significantly decreased after rotation to methylprednisolone, without an increase in the intensity of emesis (NRS: 2.63 vs. 2.08, $p = .104$) (Table 3). Complete resolution of hiccups occurred in 34 (85%) of the 40 patients after methylprednisolone replaced dexamethasone in the next chemotherapeutic cycle (Fig. 2). In the six patients whose hiccups persisted after methylprednisolone rotation, there was no significant difference in hiccup intensity between cycles.

Of the 34 patients who showed complete resolution of hiccups after rotation, 25 (73.5%) showed hiccup recurrence after dexamethasone re-administration. Table 4 shows a comparison of the results between baseline cycle and re-administration cycle in these 34 patients. Hiccup intensity (NRS: 5.24 vs. 2.44, $p < .001$) and duration (66.43 minutes vs. 22.00 minutes, $p = .033$) after dexamethasone re-administration were significantly reduced compared with baseline values.

Imbalance of DIH Incidence Between Males and Females

Of the 40 eligible patients who were recruited from eight cancer centers, 38 (95%) were male. Both of the female patients showed complete resolution of hiccups after methylprednisolone rotation. Hiccups recurred in one of the two female patients after dexamethasone re-administration.

Table 4. Differences in symptom severity depending on chemotherapy schedule in patients whose hiccups recurred ($n = 34$)

	Baseline cycle		Re-administrated cycle		
Variable	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**	*p*
Hiccups	5.24 (2.34)	4.42–6.05	2.44 (2.57)	1.66–3.34	<.001
Hiccup duration (minutes)	66.43 (159.13)	14.31–122.56	22.00 (95.26)	−8.97–51.97	.033
Emesis	2.65 (2.42)	1.89–3.36	2.00 (2.02)	1.42–2.68	.096

Abbreviations: CI, confidence interval; SD, standard deviation.

Discussion

This study is the first to demonstrate that DIH during chemotherapy can be controlled without loss of antiemetic efficacy by switching from dexamethasone to methylprednisolone. Patients receiving chemotherapy often experience hiccups. Vardy et al. reported that 25% of patients with cancer had hiccups after dexamethasone administration [17]. Liaw et al. showed that more than 40% of patients treated with cisplatin had cisplatin-induced hiccups [4]. Hiccups in patients in this study are presumed to be DIH because 90% of hiccups disappeared after discontinuation of dexamethasone. The drawback to ceasing dexamethasone in DIH is decreased protection against emesis.

We previously reported that switching from dexamethasone to methylprednisolone appeared to be a useful therapeutic method for patients with cancer who have DIH. However, information about the severity of hiccups and emesis was unavailable, and the patient cohort was very small ($n = 5$) [9]. The present study clearly shows that median hiccup intensity improved significantly (NRS: 5.38 vs. 0.53; $p < .001$) and no statistical differences were found in terms of antiemetic effect (NRS: 2.63 vs. 2.08; $p = .104$). Our findings suggest that the practice of switching from dexamethasone to methylprednisolone could be useful for resolving DIH.

The disappearance of DIH after replacement of dexamethasone with methylprednisolone may be attributable to differential permeability of the blood brain barrier (BBB) to different corticosteroids. As a fluorinated corticosteroid, dexamethasone is lipophilic and can permeate the BBB. Dexamethasone is thought to cause hiccups by stimulating the central part of the hiccup reflex arc and lowering the synaptic threshold in the midbrain [3]. Hence, it is possible that the decreased permeability of the BBB to methylprednisolone contributes to the resolution of hiccups.

We also found an overwhelming predominance of male patients with DIH. Although patients were recruited retrospectively, 38 (95%) of the 40 patients were male. In a previous report, we described a similar finding [9]. Other studies of hiccups proven or assumed to be caused by dexamethasone administration also found male dominance [4, 17, 18]. The sex difference in incidence must stem from the mechanism of action of dexamethasone. Laboratory studies suggest the existence of sex differences in the binding affinity of dexamethasone in various brain structures and differences in the distribution of corticosteroid receptors in the brain [19–22]. The hypothalamus, which is the central area for hiccups, showed greater affinity for corticosteroids in male rats than in female rats [19]. Thus, the predominance of hiccups in male patients may stem from sexual dimorphism in dexamethasone binding affinity in the brain. Further research is warranted to investigate the mechanism of DIH.

Our study had more detailed information on hiccup intensity and duration per episode compared with other hiccup-related studies [4, 9, 23]. The recruited patients experienced moderate hiccup severity (median NRS: 5). However, we presume that additional patients may experience mild hiccups, which may be regarded as a negligible symptom by both patients and physicians.

An intriguing finding of our study was that hiccups recurring after dexamethasone re-administration were milder than the hiccups in the initial cycle (mean NRS: 5.38 vs. 2.50; $p < .001$). There are two possible explanations for this. Dexamethasone may not be the actual cause of hiccups. Liaw et al. reported that hiccups persisted in 11% of patients after discontinuation of dexamethasone during chemotherapy [4]. This suggests that dexamethasone may not always be the causative agent for hiccups in patients with cancer on chemotherapy. Alternatively, patients may acquire tolerance to DIH during chemotherapy. In this study, chemotherapeutic regimen and all antiemetics except corticosteroid were the same as for the previous cycle. Thus, we hypothesized that tolerance to dexamethasone was developed by repetitive administration. Further studies are needed to address this issue.

Some researchers argue that hiccups are caused mainly by platinum agents, because cisplatin is known to induce hiccups [21]. Liaw et al. asserted that cisplatin and dexamethasone have synergistic stimulatory effects on the hiccup reflex arc [4]. In addition, most patients in our study ($n = 34$, 85%) received platinum-containing regimens. However, the apparent association between cisplatin and hiccups may just be coincidental, considering that platinum-containing agents are a universal treatment in chemotherapy. Furthermore, hiccups developed in six patients (15%) in the present study who did not receive platinum agents. Investigations of the apparent synergism between cisplatin and dexamethasone in hiccup development are needed.

Our study has several limitations that are inherent to retrospective studies. Information about quality of life, time of symptom evaluation, and time from dexamethasone administration to hiccup development was unavailable. If interval between development of symptom and evaluation time were too long, recall bias might have occurred. Another limitation is that the possibility of placebo effect associated with symptom improvement by methylprednisolone rotation could not be excluded. The only way to address this issue would be to per-

form a randomized controlled trial comparing placebo with methylprednisolone. However, the study would be very expensive and lengthy because hiccups develop in only a minority of patients. In addition, selection bias could not be excluded about male predominance of DIH.

Conclusion

DIH during chemotherapy could be controlled by rotating between dexamethasone and methylprednisolone. No statistical differences were found in terms of antiemetic effect. We also identified male predominance of DIH. Further prospective trials about DIH, including optimal doses of methylprednisolone, are warranted.

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Gyeong-Won Lee, M.D., and Sung Yong Oh, M.D., contributed equally to this work.

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Disclosures

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